

REMARKS

Examiners Steadman and Prouty are thanked for their courtesy in extending a personal interview to the inventors, Drs. Arini and Coppolecchia, and the undersigned on October 28, 2004. Each of the outstanding rejections was discussed. It was indicated that claim 81 would be represented as a new claim to recite an active culturing step and to provide a culturing time sufficient to reach the 95% level of tc-uPA without particular essential conditions. The claimed invention was discussed in the context of the references of record. The Examiners acknowledged the unexpected results of the claimed method and suggested that the benefits afforded by these unexpected results would be favorably considered in a response to the rejection. Regarding the secondary rejections under §103(a), the examiners indicated that if the primary rejection over the references of Okabayashi et al. and Zang et al. was overcome, the secondary rejections would also likely be overcome as well.

The Examiner's comments in paragraphs 1-7 of the Office Action are acknowledged. In response to paragraph 8 of the Office Action, the applicants will identify all trademarks, as such, in the specification.

In paragraph 9 of the Office Action, claims 81-90 were rejected under 35 U.S.C. §112, second paragraph, for failing to particularly point out and distinctly claim the subject matter that the applicant regards as the invention.

Reconsideration is requested in view of this Amendment.

Claims 1-92 have been canceled and new claims

93-111 have been presented in this Amendment. The newly added claims have been drafted to avoid the formal grounds of rejection. New independent Claims 93 and 102 now recite a cultivation step and new claim 93 recites that the process is carried out until the culture contains at least 95% of the total urokinase as catalytically active tc-uPA. New claim 102 recites that the process is carried out for a period of at least 120 hours. These claims now point out the essential steps of the process.

The cancellation of claims 86 and 87 has rendered moot the rejection set forth in paragraphs 9b and 9c of the Office Action. For these reasons, it is requested that this ground of rejection not be applied against the newly presented claims.

In paragraph 10 of the Office Action, claims 81-90 were rejected under 35 U.S.C. § 112, first paragraph on the basis that the test data of record showed that a culture time of 96 hours was necessary to achieve 95% of two chain urokinase.

Reconsideration is requested.

The applicants' position regarding the minimum time to reach 95% of two chain urokinase is that the test data in the Declaration Under 37 CFR § 1.132 does not limit the invention as noted in the prior Amendment. However, in order to eliminate this as an issue, new claim 102 points out a culture time of 120 hours and new claim 93 points out that the culturing step is carried out until a level of 95% of two chain urokinase is achieved. Both of these claims are definite and are supported by the specification at page 6, line 20 ("120 hours") and page 9, line 14 ("95%"). The term "mature protein" as used on page

9, line 13 points out the two chain form of urokinase as pointed out at page 3, lines 16-17 of the present specification. The dependent claims point out preferred features of the invention and these claims are also believed to be in proper form.

Since the claims that explicitly point to a culture time of less than 96 hours have been canceled, it is believed that this ground of rejection has been rendered moot and it is requested that this ground of rejection not be applied against the newly presented claims.

In paragraph 11 of the Office Action, claims 81-85 and 87-89 were rejected under 35 U.S.C. §103 as being unpatentable over Okabayashi et al. (Okabayashi) in view of the state of the art as represented by Zang et al. (Zang).

Reconsideration is requested.

The Okabayashi reference is concerned with urokinase production and is silent as to the production of two-chain urokinase. It is readily apparent that: (a) this reference does not suggest the use of a culturing time of 120 hours in the presence of a butyrate as pointed out in new claim 93 or the step of new claim 102 of carrying out of the culturing step in the presence of butyrate until the production of 95% of two chain urokinase is achieved. Zang does mention that urokinase production was stable over several months in the absence of butyrate but provides no guidance as to what happens in the presence of butyrate.

The data of record in the Declaration Under 37 CFR§1.132 provides information about the unpredictable effect of butyrate on the production of two chain urokinase. That data shows that at 24 hours (the time disclosed by Okabayashi) the two chain urokinase is present at about 67% of the total urokinase. As the culturing time progresses, the amount of two chain urokinase present increases to more than 95% at 120 hours. This selective increase in the amount of two chain urokinase is only found under the novel conditions disclosed only by the present applicants. It is quite unexpected based on the teachings of the cited prior art. The dependent claims are also patentable for the reasons advanced in support of the main claims

In the Office Action, the Examiner pointed out that it was his position that the increase in the amount of two chain urokinase was "inherent" in the process conditions suggested by the claimed combination. When the issue of inherency arises in a determination of patentability, the issue is properly limited to an inquiry of what is inherent in the "old" procedures of the prior art and not in the combination that is synthesized as a result of the Examiner's analysis of a patent applicants specification. In this regard, the Examiner is invited to consider the decision in Ex parte Stricker, 56 USPQ2d 1723 (Bd. Pat App. & Intf. 2000) where it was noted that "inherency and obviousness were like oil and water-they do not mix well" and that claimed subject matter may be anticipated based on inherency but that obviousness implies that there is a difference between the claimed subject matter and the prior art. Where there is a difference, inherency is not a substitute for the determination of obviousness. Continental Can Co. USA v. Monsanto Co. 20 USPQ2d 1746 (Fed. Cir. 1991).

It is also important to note that the combination of references is not supported by a teaching or suggestion in the prior art to combine the separate references. The only reason to combine the references is the applicants' use of butyrate in a prolonged culture cycle which is not found in a single prior art reference. If either of the cited references mentioned the production of two chain urokinase, the argument could be advanced that the cited references make out a prima facie case of obviousness, but that is not the factual record that is supported by the explicit teachings of the cited references. Based on the data of record in the Declaration Under 37 CFR§1.132, it is believed that the applicants have provided a record that points to the patentability of the newly presented claims. For these reasons, it is requested that this ground of rejection be withdrawn.

Chuppa et al. and Paques were cited in combination with Okabayashi and Zang as a basis for the rejection of claims 86 and 90. As noted above, claims 86 and 90 have been canceled and the newly presented claims which point out the optimum temperatures are claims 98, 99, 107 and 108. These claims are patentable because the secondary references which show the obviousness of certain process conditions are not processes that are concerned with the selective production of two chain urokinase in the presence of butyrate. The same observation may properly be made for the pH and filtering step of claims 101 and 111. For these reason, it is requested that the dependent claims also be favorably considered.

An early and favorable action is earnestly
solicited.

Respectfully submitted,



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